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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/087,473	03/01/2002	Melissa K. Carpenter	090/003C	1663

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GERON CORPORATION
230 CONSTITUTION DRIVE
MENLO PARK, CA 94025

EXAMINER	
TON, THAIAN N	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 12/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/087,473	CARPENTER ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-11,13-15,17,18 and 23-29* is/are pending in the application.

4a) Of the above claim(s) *24-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-11,13-15,17,18 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' Amendment, filed 9/15/04, has been entered. Claims 3, 12, 16, and 19-22 have been cancelled. Claims 23-29 have been added. Claims 1, 2, 4-7, 13-15 have been amended. Claims 1, 2, 4-11, 13-15, 17-18 and 23-29 are pending.

Newly submitted claim 29 is directed to an invention that is independent or distinct from the elected invention for the following reasons: the claim is found to correspond to Group II of the Restriction Requirement, mailed 3/19/04. Since applicant has received an action on the merits for the Group I, claim 29 is withdrawn from consideration as being directed to a non-elected invention.

Newly submitted claims 24-28 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the claims are directed to directly differentiating hES cells to hepatocytes. The originally presented invention is directed to directly differentiating hES cells into neurons or glial cells. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 24-28 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 1, 2, 4-11, 13-15, 17-18 and 23 are under current examination.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. See p. 19, line 4.

Response to Arguments

The prior rejection of claims 4, 5, and 7, under 35 USC 112, 2nd ¶ is withdrawn in view of Applicants' amendments to the claims.

The prior rejection of claims 19-20 under 35 USC § 102 (b) is rendered moot in view of Applicants' cancellation of the claims.

The prior rejection of claims 1-10 and 12-20 under 35 USC § 103 is withdrawn in view of Applicants' arguments and/or amendments to the claims.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

The prior rejection of claims 2-10, 19 and 20 for obviousness-type double patenting over co-pending application 10/039,956 is withdrawn in view of Applicants' cancellation of the claims.

The prior rejection of claims 1-5, 7, 8, 10-20 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 23-31 of copending Application No. 09/888,309 is withdrawn in view of the claims being withdrawn from consideration.

The prior rejection of claims 1, 2, 7, 12-17, 19, 20 as being provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3, 4, 6-8, 12, 13 of copending Application No. 09/994,440 is maintained for reasons of record. Applicants state that they will file a terminal disclaimer in one of the applications or otherwise address the issue once the Office and Applicants agree on what subject matter will be covered in each application. Because the terminal disclaimer has not been made of record, the rejection is maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4-11, 13-15, 17-18 and 23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Vas-Cath Inc. v. Mahurkar 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that, "[A]pplicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." *Vas-Cath Inc. v. Mahurkar,* 19USPQ2d at 1117. The specification does not, "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." *Vas-cath Inc. v. Mahurkar*, 19USPQ2d at 1116.

The instant specification fails to provide adequate written description for the claimed invention because it fails to describe how to make cell populations, for the breadth claimed, which are at least 75% homogenous, as encompassed by the claims, to indicate that Applicants had possession of the claimed invention. The claimed invention as a whole is not adequately described if the claims require

essential or critical elements which are not adequately described by the specification, and which are not conventional in the art as of Applicants' effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics, (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. See Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). In the instant case, the claimed embodiments of any cell population that is at least 75% homogenous, and is produced by differentiating hES cells, lacks a written description. The specification fails to describe how to produce cell populations that are at least 75% homogenous from hES cells. For example, the breadth of the claims encompasses any cell type, but one of skill could not envision all these cell types, and further could not envision how to produce such cell types from the specification as provided. For example, the claims encompasses producing hematopoietic stem cells by the claimed methods, but the specification fails to adequately describe the essential or critical elements by which the skilled artisan would require in order to produce a 75% homogenous population of hematopoietic stem cells from ES cells, as encompassed by the methods. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel,* 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class. The specification only provided the bovine sequence.

Applicant is reminded that *Vas-Cath* makes clear that the written description of 35 U.S.C. 112 is severable from its enablement provision [see p. 1115].

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4-11, 13-15, 17-18 and 23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to methods for producing a population of cells that at least 75% homogenous for a particular cell type comprising: providing a suspension of undifferentiated hES cells that is essentially free of feeder cells, plating and culturing the suspended cells on a solid surface so that they differentiate without

forming embryoid bodies; and harvesting differentiated cells from the solid surface, wherein at least 75% of the harvested cell population is homogenous for said cell type. In further embodiments, the specification is directed to culturing hES cells on a solid surface in an environment essentially free of feeder cells, changing the medium used to culture the cells so that they differeniate before there is overgrowth or formation of colonies, and harvesting differentiated cells from the solid surface, whereby at least 75% of the cells are homogenous for a particular cell type. In specific embodiments, the differentiated cells are committed to the neuroectoderm lineage, and specifically they are neurons or glial cells.

The specification teaches that pluripotent primate stem (pPS) cells are typically cultured on a layer of feeder cells that support the cells, for example, by the production of factors which promote the cell survival, proliferation, or inhibit differentiation. These feeder cells are typically fibroblast types of cells, often derived from embryonic or fetal tissue (see p. 11, lines 32-37). The specification teaches that pPS cells can be grown in conditioned medium, for example, fibroblast-like cells (see pp. 14-15). The working examples of the specification teach that conditioned medium was prepared from primary mouse fibroblasts (mEF) and the undifferentiated hES cells were grown in wells coated with Matrigel® [Example 1].

The state of the art of culturing human ES cells is such that it is generally supported that fibroblast feeder layers provide factors which are required for the maintenance of undifferentiated state. For example, Lim *et al.* [**Proteomics**, 2:1187-

1203(2002)] teach the proteome analysis of conditioned medium from mouse embryonic fibroblast feeder layers to characterize the environment that supports the growth of undifferentiated human ES cells, and to identify factors critical for their independent growth. See *Abstract.* Lim state that, "Despite many years of using mouse embryonic fibroblast cells as feeder support of human ES cells, it is still not clear what these cells provide for their clients. The interaction between these two cell types might take place *via* factors secreted into the medium or into extracellular matrix as well as through membrane-bound proteins." See p. 1188, 1st ¶. Lim teach that by utilizing proteomic analysis, unexpected results identify many known intracellular proteins, and that further analysis using serum-containing medium in the presence of ES cells, and using other cell types for feeder layers will be required. See p. 1203, 1st ¶, #4. The specification fails to provide any guidance or teachings as to specific factors which would allow hES cells to be propogated in an undifferentiated state under feeder-free conditions, other than using fibroblast-conditioned medium, and the state of the art clearly shows that these factors are yet to be determined. The state of the art is replete with teachings to show that in the absence of feeder cells, ES cells either differentiate or die. See Thomson (Reference BC, in Applicants' IDS, filed 5/4/04). Thomson teach the derivation of a cloned cell line from a rhesus monkey that remains undifferentiated when grown on mouse embryonic fibroblast feeder layers, but differentiate or die in the absence of the fibroblasts (see p. 7844, *Abstract*). Particularly, Thomson *et al.* state that in the

absence of the feeder layers, soluble human leukemia inhibitory factor (LIF) fails to prevent the differentiation of the cells, and that the factors that fibroblasts produce to prevent the differentiation of the cells is yet unknown (see p. 7847, 1st column, 2nd paragraph). Thomson *et al.* further state that human inner cell mass-derived cells were cultured in the absence of feeder layers failed to survive beyond 2 passages (see p. 7848, 1st paragraph). The instant specification is found to be enabling only with regard to culturing hES cells under feeder-free conditions in the presence of an extracellular matrix and fibroblast conditioned medium.

The specification fails to provide any specific guidance or teachings to enable the breadth of the claims, which is to produce a population of cells that is at least 75% homogenous from hES cells. The specific working examples of the specification fail to enable the claimed invention for the following reasons: claim 1 and its dependent claims are directed to methods of producing populations of cells which are at least 75% homogenous for a particular cell type by 1) preparing undifferentiated hES cells cultured in feeder-free conditions, 2) plating and culturing the cells on a solid surface so that they do not form embryoid bodies and 3) harvesting the differentiated cells. In further embodiments, the differentiated cells are neural cells. Example 5 of the specification is drawn to direct differentiation of hES cells to neurons without forming embryoid bodies. The specification provides various test factor groups and mixtures of the groups to culture the cells in, and then analyze the resulting differentiated cells. See Table 4. Claim 2 and its

dependent claims are directed to methods for producing cells that are at least 75% homogenous for a particular cell type by culturing hES cells on a solid surface, and changing the medium used to culture the cells so that they differentiate without overgrowth or formation of colonies, and then harvesting the cells from the solid surface. Example 2 teaches these methods by culturing rhesus and hES cells on coverslips treated with poly-ornithine and then maintaining the cells in medium. The cells were then tested for markers characteristic of neurons and astrocytes. It was found that in these cultures, rhesus ES cells contained neurons that ranged from 49-93% and hES aggregates contained 60-80% neurons. See p. 27, lines 30-37.

The specification fails to provide an enabling disclosure to show that the cells produced under any of these conditions provide more than 75% homogenous cell populations. The specification fails to provide specific guidance as to what factor, or factors, would be used in order to differentiate hES cells, under the claimed conditions, which would result in a 75% homogenous cell population and it is well-known in the art that directed differentiation of ES cells is neither routine nor predictable. For example, Du *et al.* [**Stem Cells and Development**, 13:372-381 (2004)] review the state of the art of directing the differentiation of ES cells to neural cells. Du teach that when not allowed to aggregate, hES cells to neural cells had very low efficiency, and that neural differentiation of human ES cells usually involves aggregation of the ES cells. Further, they state that when Carpenter *et al.* used traditional mouse ES cell protocols (utilizing rentinoic acid) to derive neural

precursors, wide developmental stages of neural cells were found. See p. 376, 1st column, last ¶. The instant specification teaches that the hES cells differentiated into cells which expressed markers from neurons and astrocytes, however, the specification fails to provide sufficient teachings to show that these cells are indeed a homogenous population, and not, as stated by Du, a population of cells with a wide developmental stage of neural cells. Du further discuss that factors such as cell culture media, supplements and morphogens are factors which significantly affect the resulting differentiated cells. See p. 377, 2nd column. The breadth of the claims are directed to the generation of any population of cells that is homogenous for 75% of a particular cell type. The instant specification fails to enable the breadth of this claim, and fails to provide specific guidance to enable it. Because the state of the art of ES cell differentiation is found to be unpredictable, and particularly, with regard to specific embodiments, that hES cells differentiation to neural cells requires particular specific guidance with regard to specific factors and morphogens to produce such a homogenous cell population, the lack of teaching or guidance provided by the specification for producing such cells, it would have required undue experimentation for one of skill in the art to practice the claimed methods.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Amy Nelson, Acting SPE of Art Unit 1632, at (571) 272-0804. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

tnt
Thaian N. Ton
Patent Examiner
Group 1632

Joe Woitach
AU1632